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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/685,031 | 10/14/2003 | Qi Han | BMS-PH-7164(C) | 4881 |
| 909 | 7590 | 07/08/2004 | EXAMINER | |
| PILLSBURY WINTHROP, LLP | | | KJFLE, BRUCK | |
| P.O. BOX 10500 | | | ART UNIT | |
| MCLEAN, VA 22102 | | | PAPER NUMBER | |
| | | | 1624 | |
| DATE MAILED: 07/08/2004 | | | | |

Please find below and/or attached an Office communication concerning this application or proceeding.

| | | | |
|------------------------------|------------------------|---------------------|--|
| Office Action Summary | Application No. | Applicant(s) | |
| | 10/685,031 | HAN ET AL. | |
| | Examiner | Art Unit | |
| | Bruck Kifle, Ph.D. | 1624 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 October 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-20 is/are pending in the application.
- 4a) Of the above claim(s) 13-16 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-12 and 17-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-11, 13, 16 and 18-20, drawn to compounds of formula I, pharmaceutical compositions and method of use of formula (I) wherein ring B represents benzodiazepin-2-one (see examples 1-8 and 10-15), classified in class 540, subclass 509, and, class 514, subclass 221.
- II. Claims 1-12 and 17-20, drawn to compounds of formula I, pharmaceutical compositions and method of use of formula (I) wherein ring B represents dibenzoazepinone (see example 9), classified in class 540, subclass 522, and, class 514, subclass 212.04.
- III. Claims 1-20, drawn to compounds, pharmaceutical compositions and method of use of formula (I) not falling under groups I and II above, but generically embraced by the claims, i.e., wherein ring B is NOT the dibenzoazepinone or benzodiazepinone core, classified depending on the nature of ring B. Should Applicants elect this group an election of a specific group B is required.

The inventions are distinct, each from the other because of the following reasons:

Groups I-III are drawn to structurally dissimilar compounds. They are made and used independently. They are independent and patentably distinct.

If, say compounds of Group I, were anticipated, applicants would not acquiesce in the rejection of Group II or III thereover or vice-versa. They are patentably distinct.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, and because the search

Art Unit: 1624

required for Group I is not required for Groups II or III, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Hans-Peter Hoffmann on July 1, 2004 a provisional election was made with traverse to prosecute the invention of group II, claims 1-20, reading on compounds, compositions and methods of use of compounds wherein ring "B" represents dibenzoazepinone. Affirmation of this election must be made by applicant in replying to this Office action. Claims 13-16 along with subject matter not falling under elected group II is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Improper Markush Rejection

Claims 1-11 and 18-20 are rejected as being drawn to an improper Markush group, that is, the claims lack unity of invention. Ring B is defined in such a way that it keeps changing the core of the compound that determines the classification. By changing the value of B, several patentably distinct and independent compounds are claimed. In order to have unity of invention the compounds must have "a community of chemical or physical characteristics" which justify their inclusion in a common group, and that such inclusion is not repugnant to principles of scientific classification" In re JONES (CCPA) 74 USPQ 149 (see footnote 2). The structural

Art Unit: 1624

formula (I) does not have a significant structural feature that is shared by all of its alternatives which is inventive. Compounds embraced by formula (I) are so diverse in nature that a prior art anticipating a claim with respect to one member under 35 USC 102 would not render obvious the same claim under 35 USC 103. This is evidentiary of patentably distinct and independent inventions.

Limiting the claims to the elected group would overcome this rejection.

Claim Rejections - 35 USC § 112

Claims 1-11 and 17-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- i) The term “prodrug” is indefinite because one cannot tell which prodrug is intended and what this prodrug looks like. Claims 2-4 and 6 lack antecedent basis in claim 1 for the “prodrug” and “pharmaceutically acceptable salt.”
- ii) The term “carbocycle” is indefinite. A clarification is required. It is not known what degree of saturation is intended and what kind of a ring is intended (monocyclic, polycyclic, bridged, fused, etc.)
- iii) The group “5 to 10 membered heterocycle” is indefinite because it is not known how many rings are present and what the degree of saturation of such a ring is.
- iv) The group C₆-C₁₀ aryl is improper. It is suggested to replace this with “phenyl or naphthyl” because there are no C₇, C₈ or C₉ aryl groups.

Art Unit: 1624

v) In claim 19, one cannot say which disorders are being treated and which ones are not. One skilled in the art cannot say for sure whether a neurological disorder is associated with β -amyloid production or not. A clarification is requested.

vi) In claim 20, it is unclear what is accomplished by inhibiting γ -secretase activity and who the host is that needs inhibiting γ -secretase.

vii) In claim 11, in page 178, X is defined as empty boxes. Appropriate correction is required.

Claim 19 is rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for treating any and all neurological disorders associated with β -amyloid production.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: The claim is drawn to treating any and all neurological disorders associated with β -amyloid production.

2) The state of the prior art: There are no known compounds which have been demonstrated to treat the myriad of disorders embraced by the term "neurological disorders". Alzheimer's disease is treated, albeit not successfully, using acetylcholine esterase inhibitors. A neurological disorder is not a single disease but embraces disease that are not related or even "opposites"; tumors and

Art Unit: 1624

non-tumors are covered and diseases that are not treatable pharmacologically are also embraced (e.g. Down's syndrome).

3) The predictability or lack thereof in the art: It is presumed in the treatment of the diseases claimed herein there is a way of identifying any and all of the neurological disorders associated with β -amyloid production. There is no evidence of record which would enable the skilled artisan in the identification of the disorders treatable herein. The notion that a neurological disorder can be treated generally is contrary to current medical understanding. The skill in this art is low relative to the difficulty of the task.

4) The amount of direction or guidance present and 5) the presence or absence of working examples: There are no doses present for treatment of the disorders recited.

6) The breadth of the claims: The claims are drawn to disorders that are not related and whose treatment is unknown.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan for the many reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims.

Claim 20 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which

Art Unit: 1624

it is most nearly connected, to make and/or use the invention. This claim is drawn to a method of inhibiting γ -secretase activity. The specification fails to teach any benefit to be gained from such actions. Is extensive experimentation required on the part of a potential infringer to determine if his use of Applicants' inhibitor falls within the limitations of applicants' claim? *In re Kirk and Petrow*, 153 USPQ 48 (CCPA 1967). As the Supreme Court said in *Brenner v. Manson*, 148 USPQ at 696: "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." As U.S. Court of Customs and Patent Appeals stated *In re Diedrich* 138 USPQ at 130, quoting with approval from the decision of the board: "We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates."

Claims 1-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to the invention. The specification is not adequately enabling for the scope of the compounds claimed. The only compound made is that of claim 17. This does not give a reasonable assurance that all, or

Art Unit: 1624

substantially all of the compounds that could be made are useful. The claims are not drawn in terms of a recognized genus but are directed to a more or less artificial selection of compounds.

There is no reason why a claim drawn in this way should not be limited to those compounds which are shown to be useful. An Applicant is not entitled to a claim for a large group of compounds merely on the basis of a showing that a single compound is useful and a general suggestion of a similar utility in the others.

Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

Also, see *In re Surrey* 151 USPQ 724, regarding sufficiency of a disclosure for a Markush group, and MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the instant pharmaceutical arts. Note in *Surrey*, in which testing done on a group of homogeneous compounds having the same core was deemed NOT sufficient to support claims to various hetero groups of a much narrower range than is being claimed herein and located at only one position in the formula. The instant scope is enormous; therefore one compound within its scope is not remotely representative of such a scope. See MPEP 2164.03.

Claim 17 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Art Unit: 1624

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruck Kifle, Ph.D. whose telephone number is 571-272-0668.

The examiner can normally be reached on 9:30-6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund J. Shah can be reached on 571-272-0674. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.



Bruck Kifle, Ph.D.
Primary Examiner
Art Unit 1624

BK
July 1, 2004